

Claims:

1. A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular glutathione (GSH) level.
- 5 2. The method of claim 1, wherein the at least one gene involved in regulating the intracellular GSH level comprises glutamate-cysteine ligase (GCL), glutathione synthetase (GSS), glutathione peroxidase (GPX) and/or glutamate/cysteine exchange transporter (system Xc⁻) gene.
3. The method of claim 2, wherein GCL comprises the glutamate-cysteine ligase
10 modulating subunit (GCLM).
4. The method of claim 2, wherein GPX comprises GPX1.
5. The method of any one of claims 1 to 4 further comprising comparing the level of expression determined for a subject with the level of expression of the corresponding at least one gene for a subject or subject population not affected by the mental disorder; wherein a
15 difference of more than 20 percent indicates that the subject is affected or at risk of being affected by the mental disorder.
6. The method of any one of claims 1 to 5, wherein the level of expression is determined by measuring the level of transcription of the at least one gene.
7. The method of any one of claims 1 to 6, wherein the level of transcription is determined
20 by at least one oligonucleotide or polynucleotide able to bind to the transcription product of the at least one gene.
8. The method of claim 6 or 7, wherein the level of transcription is determined by techniques selected from the group of Northern blot analysis, reverse transcriptase PCR, real-time PCR, RNase protection and microarray analysis.
- 25 9. The method of any one of claims 1 to 5, wherein the level of expression is determined by measuring the level of protein expressed by the at least one gene.
10. The method of claim 9, wherein the level of protein is determined by antibodies, antibody derivatives, or antibody fragments.

11. The method of claim 10, wherein the level of protein is determined by Western blotting, FACS, immunohistochemistry, ELISA, ELISPOT utilizing an antibody, an antibody derivative, or an antibody fragment.
12. A method for diagnosis of a mental disorder comprising determining the level of activity
5 of at least one protein involved in regulating the intracellular GSH level.
13. The method of claim 12, wherein the at least one protein comprises GCL, gamma-glutamyltransferase (GGT) and/or system Xc⁻.
14. The method of claim 12 or 13, wherein GCL comprises the glutamate-cysteine ligase catalytic subunit (GCLC).
- 10 15. The method of any one of claims 12 to 14 further comprising comparing the level of activity determined for a subject with the level of activity of the corresponding at least one protein for a subject or subject population not affected by the mental disorder, wherein a difference of more than 10 percent indicates that the subject is affected or at risk of being affected by the mental disorder.
- 15 16. The method of any one of claims 12, 13 or 15, wherein the level of activity of system Xc⁻ is determined by measuring [³⁵S] cystine uptake.
17. A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular GSH level and determining the level of activity of at least one protein involved in regulating the Intracellular
20 GSH level.
18. The method of claim 17, wherein at least one gene involved in regulating the intracellular GSH level comprises GCL, GCLM, GPX, GPX1, GSS and/or system Xc⁻ gene and wherein the at least one protein comprises GCL, GCLC, GGT and/or system Xc⁻.
19. The method of claim 17 or 18, which further comprises determining the level of
25 intracellular GSH levels.
20. The method of any one of claims 17 to 19, wherein the level of expression of GCLM, the level of activity of GCL and the intracellular level of GSH is determined.

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21. The method of claim 20, wherein a decreased expression of GCLM and a negative correlation between GCL activity and GSH levels indicates that the subject is affected or at risk of being affected by the mental disorder.
22. The method of any one of claims 12 to 15 or 19 to 20, wherein the level of activity of
5 GCL is determined by measuring the amount of ^{14}C - γ -glutamyl-aminobutyric acid.
23. A method for diagnosis of a mental disorder comprising determining the plasmatic level of at least one amino acid.
24. The method of claim 23, wherein the plasmatic level of cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine is determined.
- 10 25. The method of claim 23 or 24 further comprising comparing the plasmatic level of cysteine and/or homocysteine of a subject with the levels of a subject or subject population not affected by the mental disorder; wherein a difference of more than 5 percent indicates that the subject is affected or at risk of being affected by the mental disorder.
- 15 26. A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular GSH level and determining the plasmatic level of at least one amino acid.
- 20 27. The method of claim 26, wherein at least one gene involved in regulating the intracellular GSH level comprises GCL, GCLM, GPX, GPX1, GSS and/or system Xc⁻ gene, and wherein the at least one amino acid comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.
28. The method of claim 26 or 27, wherein the level of expression is determined for GCLM and the plasmatic levels of cystine and glutamate are determined.
- 25 29. The method of claim 28, wherein a decreased expression of GCLM and an absence of correlation between cystine and glutamate levels indicates that a subject is affected or at risk of being affected by the mental disorder.
30. A method for diagnosis of a mental disorder comprising determining the level of activity of at least one protein involved in regulating the intracellular GSH level and determining the plasmatic level of at least one amino acid.

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31. The method of claim 30, wherein the at least one protein comprises GCL, GCLC, GGT and/or system Xc⁻ and wherein the at least one amino acid comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.
32. The method of claim 30 or 31, wherein the level of activity is determined for GGT and
5 wherein the plasmatic level of cysteinyl-glycine is determined.
33. The method of claim 32, wherein an absence of a correlation of GGT activity and the level of cysteinyl-glycine indicates that a subject is affected or at risk of being affected by the mental disorder.
34. The method of any one of claims 12, 13, 15 or 30 to 33, wherein the level of activity of
10 GGT is determined by measuring the formation of 5-amino-2-nitrobenzoate.
35. The method of any one of claims 23 to 34, wherein the level of amino acids is determined with an amino acid analyzer.
36. A method of any one of claims 23 to 35, wherein the level of the at least one amino acid is determined by HPLC.
- 15 37. A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular glutathione (GSH) level and determining the GSH level in blood.
38. The method of claim 37, wherein the level of expression is determined for GCLM.
39. The method of claim 38, wherein a decreased expression of GCLM and a decrease in
20 GSH levels indicates that a subject is affected or at risk of being affected by the mental disorder.
40. The method of any one of claims 1 to 39, wherein the method is performed *ex vivo*.
41. The method of any one of claims 1 to 40, wherein the mental disorder is selected from the group of schizophrenic disorders, affective disorders, psychoactive substance use
25 disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.
42. The method of claim 41, wherein the mental disorder is schizophrenia.

43. A composition for use in diagnosis of a mental disorder comprising at least one oligonucleotide or polynucleotide able to bind to a transcription product of at least one gene involved in regulating intracellular GSH level.

5 44. The composition of claim 43, wherein the at least one oligonucleotide or polynucleotide is able to bind to a transcription product of the GCL, GSS, GPX and/or system Xc⁻ gene.

45. The composition of claim 44, wherein GCL comprises GCLM.

46. The composition of claim 44, wherein and GPX comprises GPX1.

10 47. The composition of claim 44, wherein the oligonucleotide or polynucleotide comprises at least one sequence selected from the group consisting of SEQ ID NO. 1 to 9.

48. The composition of claim 44, comprising the oligonucleotide of SEQ ID No 3 and/or SEQ ID 4, and optionally SEQ ID NO 2 able to bind to GSS transcripts.

49. The composition of claim 44 or 46, comprising the oligonucleotide of SEQ ID No 6 and/or SEQ ID 7, and optionally SEQ ID NO 5 able to bind to GPX transcripts.

15 50. A composition for use in diagnosis of a mental disorder comprising at least one antibody, antibody derivative or antibody fragment able to bind at least one protein involved in regulating intracellular GSH level.

51. The composition of claim 50, wherein the antibody is a monoclonal antibody.

20 52. A composition for use in diagnosis of a mental disorder comprising at least one means able to determine the activity of at least one protein involved in regulating intracellular GSH level.

53. A composition of claim 51, wherein the at least one protein comprises GCL, GGT and/or system Xc⁻.

25 54. A composition for use in diagnosis of a mental disorder comprising at least one means able to determine the plasmatic level of at least one amino acid.

55. A composition of claim 54, wherein the at least one amino acid comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.

56. A composition of claim 54 or 55, wherein the means comprise an amino acid analyzer.
57. The composition of any one of claims 43 to 56 for use in diagnosis of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent
5 explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), or manic or psychotic depression.
58. The composition of any one of claims 43 to 57 for use in diagnosis of schizophrenia.
59. A kit for diagnosis of a mental disorder comprising a means for determining the level of transcription of at least one gene involved in regulating intracellular GSH level.
- 10 60. The kit of claim 59, wherein the means for determining the level of transcription comprise at least one oligonucleotide or polynucleotide able to bind to a transcription product of the GCL, GSS, GPX and/or system Xc⁻ gene.
61. The kit of claim 60, wherein GCL comprises GCLM.
62. The kit of claim 60, wherein GPX comprises GPX1.
- 15 63. The kit of claim 60, wherein the oligonucleotide or polynucleotide comprises at least one sequence selected from the group consisting of SEQ ID NO. 1 to 9.
64. The kit of any one of claims 59 to 63, further comprising a DNA sample collecting means.
- 20 65. A kit for diagnosis of a mental disorder comprising a means for determining the level of protein expressed by at least one gene involved in regulating intracellular GSH level.
66. The kit of claim 65, wherein the means for determining the level of protein comprises at least one antibody, antibody derivative or antibody fragment able to bind GCL, GSS, GPX and/or system Xc⁻.
- 25 67. A kit for diagnosis of a mental disorder comprising a means for determining the level of activity of the protein expressed by at least one gene involved in regulating intracellular GSH level.
68. A kit of claim 67, wherein the protein comprises GCL, GGT and/or system Xc⁻.

69. The kit of any one of claims 65 to 68, further comprising a protein sample collecting means.
70. A kit for diagnosis of a mental disorder comprising at least one means for determining the plasmatic level of at least one amino acid.
- 5 71. A kit of claim 70, wherein the at least one amino acid comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.
72. A kit of claim 70 or 71, wherein the means comprise an amino acid analyzer
73. The kit according to any one of claims 59 to 72, further comprising a means for collecting a biological sample.
- 10 74. The kit according to any one of claims 59 to 73, further comprising instructions for use of the kit and interpretation of the determined level of expression and/or activity.
75. The kit of any one of claims 59 to 74 for diagnosis of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder,
- 15 impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), or manic or psychotic depression.
76. The kit of any one of claims 59 to 75 for diagnosis of schizophrenia.
77. The method of any one of claims 1 to 22 and 26 to 42, wherein the determining step for measuring the level of expression and/or the level of activity of the at least one gene
- 20 and/or protein comprises the use of a kit of any one of claims 59 to 76.
78. Use of one or more proteins for the manufacture of a medicament for use in the treatment and/or prevention of a mental disorder, wherein the one or more protein is selected from the group consisting of
- a) GCL, GSS, GPX and system Xc⁻ or a fragment thereof;
- 25 b) a bioactive protein having a percentage of identity of at least 50% with the amino acid sequence of any one of the proteins of (a);
- c) a bioactive variant of any one of the proteins of (a) or (b).

79. The use of claim 78, wherein GCL comprises GCLM.

80. The use of claim 78, wherein GPX comprises GPX1.

81. Use of one or more polynucleotides for the manufacture of a medicament for use in the treatment and/or prevention of a mental disorder, wherein the one or more polynucleotide
5 comprises a sequence encoding a protein as defined in any one of claims 78 to 80, said sequence being operatively associated with a tissue specific or a constitutive promoter.

82. The use of the one or more protein of any one of claims 78 to 80 or the one or more polynucleotide of claim 81 for the manufacture of a medicament for use in the treatment and/or prevention of a mental disorder, wherein the mental disorder is selected from the
10 group of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, Intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

83. The use of one or more protein of any one of claims 78 to 80 and/or one or more
15 polynucleotide of claim 81 for the manufacture of a medicament for use in the treatment and/or prevention of a mental disorder, wherein said mental disorder is schizophrenia.

84. A pharmaceutical composition for use in prevention and/or treatment of a mental disorder comprising one or more protein as defined in any one of claims 78 to 80 and/or one or more polynucleotide as defined in claim 81 and a pharmaceutically-acceptable carrier.

20 85. A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of one or more proteins to a mammal including a human, wherein the one or more protein is selected from the group consisting of

a) GCL, GSS, GPX and system Xc^- or a fragment thereof

b) a bioactive protein having a percentage of identity of at least 50% with the amino acid
25 sequence of any one of the proteins of (a);

c) a bioactive variant of any one of the proteins of (a) or (b).

86. The method of claim 85, wherein GCL comprises GCLM.

87. The method of claim 85, wherein GPX comprises GPX1.

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88. A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of one or more polynucleotides to a mammal including a human, wherein the one or more polynucleotide comprises a sequence encoding a protein as defined in any one of claims 85 to 87, said sequence being operatively associated with a tissue specific or a constitutive promoter.
89. A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of an agent that can alter the expression of at least one gene involved in regulating intracellular GSH level.
90. The method of claim 89, wherein the at least one gene involved in regulating the intracellular GSH level comprises GCL, GSS, GPX and/or system Xc⁻ gene.
91. The method of claim 90, wherein GCL comprises GCLM.
92. The method of claim 90, wherein GPX comprises GPX1.
93. A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of an agent that can alter the activity of at least one protein involved in regulating intracellular GSH level.
94. The method of claim 93, wherein the at least one protein involved in regulating the intracellular GSH level comprises GCL, GGT and/or system Xc⁻.
95. The method of claim 94, wherein GCL comprises GCLC.
96. The method of claim, wherein GCL comprises GCLM.
97. A method for prevention and/or treatment of a mental disorder which comprises administering an effective amount of an agent that can alter the plasmatic level of at least one amino acid.
98. The method of claim 97, wherein the at least one amino acids comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.
99. The method of any one of claims 85 to 98, wherein the effective amount of the protein and/or the polynucleotide and/or the agent is administered orally, sublingually, intravenously, intramuscularly, intraarticularly, intraarterially, intramedullary, Intrathecally, intraventricularly, intraocularly, intrathecally, Intracerebrally, intracranially, respiratorally, intratracheally,

nasopharyngeally, transdermally, intradermally, subcutaneously, intraperitoneally, intranasally, enterally, or topically, or via rectal means, infusion or implant.

100. The method of any one of claims 85 to 99, wherein the mental disorder is selected from the group of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

101. The method of any one of claims 85 to 102, wherein the mental disorder is schizophrenia.

102. A method for screening for a modulator of a mental disorder comprising:

(a) determining the level of expression of at least one gene involved in regulating intracellular GSH in a sample of cells;

(b) contacting the sample of cells with a candidate agent;

(c) determining the level of expression of the at least one gene of (a) for the sample of cells of (b);

(d) comparing the levels of expression determined in (a) and (c), wherein an alteration in the level of expression of the at least one gene indicates that the candidate agent is a modulator of the mental disorder.

103. The method of claim 102, wherein the sample of cells comprise a biological sample derived from a subject affected with a mental disorder.

104. A method for screening for a modulator of a mental disorder comprising:

(a) administering a candidate agent to a non-human test animal which is predisposed to be affected or which is affected by a mental disease;

(b) administering the candidate agent of (a) to a matched control non-human animal not predisposed to be affected or being affected by a mental disease;

(c) determining the level of expression of at least one gene involved in regulating intracellular GSH in vivo or in vitro in a biological sample isolated from the animal of steps (a) and (b);

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(d) comparing the levels of expression of step (c); wherein an alteration in the level of expression of the at least one gene indicates that the candidate agent is a modulator of the mental disorder.

105. The method of any one of claims 102 to 104, wherein the at least one gene involved in
5 regulating the intracellular GSH level comprises GCL, GSS, GPX and/or system Xc⁻ gene.

106. The method of claim 105, wherein GCL comprises GCLM.

107. The method of claim 105, wherein GPX comprises GPX1.

108. A method for screening for a modulator of a mental disorder comprising:

10 (a) determining the level of activity of at least one protein involved in regulating intracellular GSH in a sample of cells;

(b) contacting said sample of cells with a candidate agent;

(c) determining the level of activity of the at least one protein of (a) for the sample of cells of (b);

15 (d) comparing the activity determined in (a) and (c), wherein an alteration in the activity of the at least one protein indicates that the candidate agent is a modulator of the mental disorder.

109. The method of claim 108, wherein the sample of cells comprise a biological sample derived from a subject affected with a mental disorder.

110. A method for screening for a modulator of a mental disorder comprising:

20 (a) administering a candidate agent to a non-human test animal which is predisposed to be affected or which is affected by a mental disease;

(b) administering the candidate agent of (a) to a matched control non-human animal not predisposed to be affected or being affected by a mental disease;

25 (c) determining the levels of activity of at least one protein involved in regulating intracellular GSH in vivo or in vitro in a biological sample isolated from the animal of steps (a) and (b);

(d) comparing the level of activity of step (c); wherein an alteration in the level of activity of the at least one protein indicates that the candidate agent is a modulator of the mental disorder.

111. A method for screening for a modulator of a mental disorder comprising:

5 (a) combining at least one protein involved in regulating the intracellular GSH level, the protein binding partner, and a candidate agent to form a reaction mixture; and

(b) determining interaction of the protein and the protein binding partner in the presence and absence of the candidate agent.

112. The method of any one of claims 108 to 111, wherein the at least one protein involved
10 in regulating the intracellular GSH level comprises GCL, GGT and/or system Xc⁻ protein.

113. The method of claim 112, wherein GCL comprises GCLC.

114. A method for screening for a modulator of a mental disorder comprising:

(a) administering a candidate agent to a non-human test animal which is predisposed to be affected or which is affected by a mental disease;

15 (b) administering the candidate agent of (a) to a matched control non-human animal not predisposed to be affected or being affected by a mental disease;

(c) determining the level of at least one amino acid in a plasma sample isolated from the animal of steps (a) and (b);

20 (d) comparing the level of the at least one amino acid of step (c); wherein an alteration in the level of the at least one amino acid indicates that the candidate agent is a modulator of the mental disorder.

115. A method of claim 114, wherein the level of cysteine and/or homocysteine in step (c) are determined.

116. A method for screening for a modulator of a mental disorder comprising:

25 (a) administering a candidate agent to a non-human test animal which is predisposed to be affected or which is affected by a mental disease;

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(b) administering the candidate agent of (a) to a matched control non-human animal not predisposed to be affected or being affected by a mental disease;

(c) determining the level of GCL activity and the levels of GSH in blood cells isolated from the animal of steps (a) and (b);

5 (d) comparing the level of GCL activity and the levels of GSH in blood cells of step (c); wherein the absence of a correlation between GCL activity and the GSH level in blood cells indicates that the candidate agent is a modulator of the mental disorder.

117. A method for screening for a modulator of a mental disorder comprising:

10 (a) administering a candidate agent to a non-human test animal which is predisposed to be affected or which is affected by a mental disease;

(b) administering the candidate agent of (a) to a matched control non-human animal not predisposed to be affected or being affected by a mental disease;

(c) determining the level of GGT activity and the level of cysteinyl-glycine in plasma isolated from the animal of steps (a) and (b);

15 (d) comparing the level of GGT activity and the level of cysteinyl-glycine in plasma of step (c); wherein a positive correlation between GGT activity and level of cysteinyl-glycine in plasma indicates that the candidate agent is a modulator of the mental disorder.

GCLM level of expression and the plasmatic levels of cystine and glutamate are determined.

118. A method for screening for a modulator of a mental disorder comprising:

20 (a) administering a candidate agent to a non-human test animal which is predisposed to be affected or which is affected by a mental disease;

(b) administering the candidate agent of (a) to a matched control non-human animal not predisposed to be affected or being affected by a mental disease;

25 (c) determining the level of glutamate and cystine in plasma isolated from the animal of steps (a) and (b);

(d) comparing the level of glutamate and cystine in plasma of step (c); wherein a positive correlation between glutamate and cystine in plasma indicates that the candidate agent is a modulator of the mental disorder.

119. The method of any one of claims 102 to 118, wherein said mental disorder is selected from the group of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

120. The method of any one of claims 102 to 119, wherein said mental disorder is schizophrenia.

121. A method for the diagnosis of a mental disorder or a predisposition therefor in a mammal, particularly in a human being, comprising determining the presence of at least one polymorphism of at least one gene involved in regulating the intracellular glutathione (GSH) level and/or GSH-oxidative stress-related gene expression, wherein said at least one polymorphism is associated with said mental disorder or predisposition therefor.

122. The method of claim 121, wherein the at least one gene involved in regulating the intracellular GSH level and/or GSH-oxidative stress-related gene expression is selected from a glutamate-cysteine ligase, modifier subunit gene (GCLM) and/or a glutathione synthetase gene (GSS).

123. The method of any one of claims 121 and 122, wherein said polymorphism is associated with low expression levels of at least one gene involved in regulating the intracellular glutathione level and/or GSH-oxidative stress-related gene expression.

124. The method of any one of claims 121 to 123, wherein the polymorphism is located within an intron, the 3' region and/or the 5' region of the at least one gene.

125. The method of any one of claims 121 to 124 comprising determining a single polymorphism in a chromosomal copy of the gene, wherein said polymorphism is associated with said mental disorder or predisposition therefor.

126. The method of any one of claims 121 to 125 comprising determining a single polymorphism in two chromosomal copies of the gene, wherein said polymorphism is associated with said mental disorder or predisposition therefor.

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127. The method of any one of claims 121 to 126 comprising determining a combination of polymorphisms in a chromosomal copy of the gene, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

5 128. The method of any one of claims 121 to 127 comprising determining a combination of polymorphisms in two chromosomal copies of the gene, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

129. The method for any one of claims 121 to 128, comprising determining a combination of polymorphisms in at least one chromosomal copy of a combination of genes, wherein said combination of polymorphisms is associated with said mental disorder or predisposition
10 therefor.

130. The method of any one of claims 121 to 129, wherein the polymorphism of the GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs2064764, rs769211, rs718873, rs718875, rs2301022,

15 (b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

131. The method of claim 130, wherein the polymorphism is

(a) rs2235971, rs3170633, rs769211 and/or rs2301022,

20 (b) in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

132. The method of claim 131, wherein the polymorphism is

(a) rs3170633

(b) in linkage disequilibrium with the polymorphism of (a), and

25 (c) selected from combinations of polymorphisms of (a) and/or (b).

133. The method of any one of claims 121 to 129 and 132, wherein the genotype of the

polymorphism rs3170633 is selected from the group consisting of the nucleotides AA, AG and/or GG.

134. The method of claim 133, wherein the genotype is GG.

135. The method of any one of claims 121 to 129, wherein a combination of polymorphisms
5 in at least one chromosomal copy of the GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs769211 and rs2301022,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

10 136. The method of any one of claims 121 to 129, wherein the polymorphism of the GSS gene is selected from the group consisting of

(a) the polymorphisms rs3746450, rs725521, rs1801310, rs2236270, rs2236271, rs2273684, rs734111, rs2025096, rs3761144,

15 (b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

137. The method of claim 136, wherein the polymorphism is

(a) rs2236270, rs2273684, rs734111, rs2025096 and/or rs3761144,

(b) in linkage disequilibrium with at least one of the polymorphisms of (a), and

20 (c) selected from combinations of polymorphisms of (a) and/or (b).

138. The method of claim 137, wherein the polymorphism is

(a) rs3761144,

(b) in linkage disequilibrium with the polymorphism of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

25 139. The method of any one of claims 121 to 129, wherein a combination of polymorphisms

in at least one chromosomal copy of the GSS gene is selected from the group consisting of

(a) the polymorphisms rs2236270, rs2273684, rs734111, rs2025096 and rs3761144,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

5 (c) combinations of polymorphisms of (a) and/or (b).

140. The method of any one of claims 121 to 129, wherein a combination of polymorphisms in at least one chromosomal copy of a combination of the GSS gene and the GCLM gene is selected from the group consisting of

10 (a) the polymorphisms rs2235971, rs3170633, rs769211, rs2301022, rs2236270, rs2273684, rs734111, rs2025096 and/or 3761144,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

15 141. The method of any one of claims 121 to 129, wherein a combination of polymorphisms in two chromosomal copies of the GCLM gene or the GSS gene is homozygous.

142. The method of any one of claims 121 to 141, wherein the polymorphism is determined by a genotyping analysis.

143. The method of claim 142, wherein the genotyping analysis comprises the use of polymorphism-specific primers.

20 144. The method of claims 142 to 143, wherein the genotyping analysis comprises a mass-spectrometric analysis.

145. The method of claims 142 to 143, wherein the genotyping analysis comprises a microarray analysis.

25 146. The method of any one of claims 121 to 145, wherein the mental disorder is selected from the group of schizophrenic disorders, affective disorders, psychoaffective substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis,

attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

147. The method of claim 146, wherein the mental disorder is schizophrenia.

148. A diagnostic composition or kit for the diagnosis of a mental disorder or a predisposition therefor in a mammal, particularly in a human being comprising at least one primer and/or probe for determining the presence of at least one polymorphism of at least one gene involved in regulating the intracellular GSH level and/or GSH-oxidative stress-related gene expression, wherein said at least one polymorphism is associated with a mental disorder or predisposition therefor.

149. The composition or kit of claim 148, wherein at least one gene involved in regulating the intracellular GSH level and/or GSH-oxidative stress-related gene expression is selected from a GCLM gene and/or a GSS gene.

150. The composition or kit of claim 148, comprising at least one primer and/or probe which hybridises to the GCLM and/or GSS gene and which allows a specific determination of said polymorphism or combination of polymorphisms.

151. The composition or kit of any one of claims 148 to 150 comprising at least one primer and/or probe for determining a single polymorphism in a chromosomal copy of the gene, wherein said polymorphism is associated with said mental disorder or predisposition therefor.

152. The composition or kit of any one of claims 148 to 151 comprising at least one primer and/or probe for determining a single polymorphism in two chromosomal copies of the gene, wherein said polymorphism is associated with said mental disorder or predisposition therefor.

153. The composition or kit of any one of claims 148 to 152 comprising a combination of primers and/or probes for determining a combination of polymorphisms in a chromosomal copy of the gene, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

154. The composition or kit of any one of claims 148 to 153 comprising a combination of primers and/or probes for determining a combination of polymorphisms in two chromosomal copies of the gene, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

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155. The composition or kit of any one of claims 148 to 154 comprising a combination of primers and/or probes for determining a combination of polymorphisms in at least one chromosomal copy of a combination of genes, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

5 156. The composition or kit of any one of claims 148 to 155, wherein the polymorphism of the GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs2064764, rs769211, rs718873, rs718875 and/or rs2301022,

10 (b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

157. The composition or kit of claim 156, wherein the polymorphism is

(a) rs2235971, rs3170633, rs2301022 and/or rs769211,

(b) in linkage disequilibrium with at least one of the polymorphisms of (a), and

15 (c) selected from combinations of polymorphisms of (a) and/or (b).

158. The composition or kit of claim 157, wherein the polymorphism is

(a) rs3170633,

(b) in linkage disequilibrium with the polymorphism of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

20 159. The composition or kit of any one of claims 148 to 155 and 158, wherein the genotype of the polymorphism rs3170633 is selected from the group consisting of the nucleotides AA, AG and/or GG.

160. The composition or kit of claim 159, wherein the genotype is GG.

161. The composition or kit of any one of claims 148 to 155, wherein a combination of polymorphisms in at least one chromosomal copy of the GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs769211 and rs2301022,

5 (b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

162. The composition or kit of any one of claims 148 to 155, wherein the polymorphism of the GSS gene is selected from the group consisting of

10 (a) the polymorphisms rs3746450, rs725521, rs1801310, rs2236270, rs2236271, rs2273684, rs734111, rs2025096, rs3761144,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

15 163. The composition or kit of claim 162, wherein the polymorphism is

(a) rs2236271, rs2273684, rs734111, rs2025096 and/or rs3761144,

(b) in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

164. The composition or kit of claim 163, wherein the polymorphism is

20 (a) rs3761144,

(b) in linkage disequilibrium with the polymorphism of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

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165. The composition or kit of any one of claims 148 to 155, wherein a combination of polymorphisms in at least one chromosomal copy of the GSS gene is selected from the group consisting of

(a) the polymorphisms rs2236270, rs2273684, rs734111, rs2025096 and rs3761144,

5 (b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

166. The composition or kit of any one of claims 148 to 155, wherein a combination of polymorphisms in at least one chromosomal copy of a combination of the GSS gene and the
10 GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs769211, rs2301022, rs2236270, rs2273684, rs734111, rs2025096 and/or rs3761144,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

15 (c) combinations of polymorphisms of (a) and/or (b).

167. The composition or kit of any one of claims 148 to 155, wherein a combination of polymorphisms in two chromosomal copies of the GCLM gene or the GSS gene is homozygous.

168. The composition or kit of any one of claims 148 to 167, further comprising an enzyme
20 for primer elongation, nucleotides and/or labelling groups.

169. The composition or kit of any one of claims 148 to 168 for the diagnosis of schizophrenic disorders, affective disorders, psychoaffective substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-
25 deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

170. The composition or kit of claim 169, wherein the mental disorder is schizophrenia.

171. A microarray for the diagnosis of a mental disorder or a predisposition therefor in a mammal, particularly in a human being, comprising a carrier having immobilised thereto at

least one probe for determining the presence of at least one polymorphism and/or of at least one combination of polymorphisms of at least one copy of a gene involved in regulating the intracellular GSH level and/or GSH-oxidative stress-related gene expression, wherein said at least one polymorphism, combination of polymorphisms and/or genotype is associated with a mental disorder or predisposition therefor.

172. A primer and/or probe or a combination of primers and/or probes for the diagnosis of a mental disorder or a predisposition therefor in a mammal, particularly in a human being for determining the presence of at least one polymorphism, and/or of at least one combination of polymorphisms of at least one copy of a gene involved in regulating the intracellular GSH level and/or GSH-oxidative stress-related gene expression, wherein said at least one polymorphism, combination of polymorphisms and/or genotype is associated with a mental disorder or predisposition therefor.

173. A pharmaceutical composition comprising one or more active ingredients which increase the intracellular GSH level and, optionally, a pharmaceutically acceptable carrier, diluent and/or adjuvant for use in the treatment and/or prevention of a mental disorder in patients having at least one polymorphism, and/or at least one combination of polymorphisms of at least one copy of a gene involved in regulating the intracellular glutathione (GSH) level and/or GSH oxidative stress-related gene expression.

174. The composition of claim 173, wherein the active ingredient is a protein selected from the group consisting of

a) GCLM and/or GSS or a fragment thereof,

b) a bioactive protein having a percentage of identity of at least 50% with the amino acid sequence of any one of the proteins of a), and

c) a bioactive variant of any one of the proteins of a) or b).

175. The composition of claim 173, wherein the active ingredient is a polynucleotide comprising a sequence encoding a protein as defined in claim 174.

176. The composition of claim 173, wherein the active ingredient is GSH or a compound increasing the intracellular GSH level.

177. The composition of any one of claims 173 to 176, wherein the patients have at least one polymorphism as defined in any one of claims 130 to 132 and 136 to 138, at least one

genotype as defined in any one of claims 133, 134 and 141 and/or at least one combination of polymorphisms as defined in any one of claims 135, 139 and 140.

178. Use of one or more active ingredients as defined in any one of claims 173 to 176 for the manufacture of a medicament which increases the intracellular GSH level for use in the treatment and/or prevention of a mental disorder in patients having at least one polymorphism, and/or at least one combination of polymorphisms of at least one copy of a gene involved in regulating the intracellular glutathione (GSH) level and/or GSH oxidative stress-related gene expression.

179. The use of claim 178, wherein the active ingredient is a protein selected from the group consisting of

a) GCLM and/or GSS or a fragment thereof,

b) a bioactive protein having a percentage of identity of at least 50% with the amino acid sequence of any one of the proteins of a), and

c) a bioactive variant of any one of the proteins of a) or b).

180. The use of claim 178, wherein the active ingredient is a polynucleotide comprising a sequence encoding a protein as defined in claim 179.

181. The use of claim 178, wherein the active ingredient is GSH or a compound increasing the intracellular GSH level.

182. The use of any one of claims 178 to 181, wherein the patients have at least one polymorphism as defined in any one of claims 130 to 132 and 136 to 138, at least one genotype as defined in any one of claims 133, 134 and 141 and/or at least one combination of polymorphisms as defined in any one of claims 135, 139 and 140.

183. Use of a compound effective against mental disorders for the manufacture of a medicament for administration to patients having at least one polymorphism, and/or at least one combination of polymorphisms of at least one copy of a gene involved in regulating the intracellular glutathione (GSH) level and/or GSH-oxidative stress-related gene expression.

184. A method of preventing and/or treating a mental disorder comprising administering a medicament which is effective against mental disorders and/or increases the intracellular GSH level to a patient having at least one polymorphism, and/or at least one combination of

polymorphisms of at least one copy of a gene involved in regulating the intracellular glutathione (GSH) level and/or GSH-oxidative stress-related gene expression.

185. A method of preventing and/or treating a mental disorder comprising administering a medicament effective against mental disorders to a patient having at least one
5 polymorphism, and/or at least one combination of polymorphisms of at least one copy of a gene involved in regulating the intracellular glutathione (GSH) level and/or GSH-oxidative stress-related gene expression.

186. The method of claims 184 or 185, wherein the medicament comprises at least one compound selected from the group consisting of

10 (a) anti-epileptic drugs selected from barbiturates and derivatives thereof, benzodiazepines, carboxamides, hydantoins, succinimides, valproic acid and other fatty acid derivatives and other anti-epileptic drugs,

(b) conventional antipsychotics and

(c) atypical antipsychotics, in which the active ingredients are present in each case in
15 free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

187. A method of screening for a modulator of a mental disorder, comprising determining the effect of a test substance on the activity of at least one copy of a gene involved in regulating the intracellular GSH level and/or GSH-oxidative stress-related gene expression,
20 wherein the at least one copy of a gene has at least one polymorphism, and/or at least one combination of polymorphisms which is associated with said mental disorder or predisposition therefor.

188. The method of claim 186, wherein the at least one polymorphism is defined as in any one of claims 130 to 132 and 136 to 138, the at least one genotype as defined in any one of
25 claims 133, 134 and 141 and/or the at least one combination of polymorphisms is defined as in any one of claims 135, 139 and 140.